Author response: BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis

van Niftrik, Christiaan H B ; Sebök, Martina ; Fierstra, Jorn

Abstract: We kindly thank Drs. Reidler and Kunz for their insightful comments regarding our article.1 The main objective was to study blood oxygen level–dependent cerebrovascular reactivity (BOLD-CVR) for crossed cerebellar diaschisis (CCD) detection. In this regard, worse clinical outcome in the CCD(+) group should indeed be interpreted with caution. Ideally, this association needs to be further investigated in a uniform stroke cohort with sequential follow-up studies. We deliberately did not comment on supratentorial stroke volume because it is an inexact measurement and does not say anything about the infarct location.2 Besides, the concept that stroke volume is highly associated with the presence of CCD in the acute phase remains debatable, as the studies mentioned in the readers' comment appeared to be in disagreement.3,4 Nevertheless, we agree that stroke location would be a better variable for an adjusted analysis. The statement made by Drs. Reidler and Kunz about "inferior cerebrovascular response indicating more severe supratentorial lesions" is, however, erroneous. We have only shown the presence of more impaired supratentorial BOLD-CVR in the CCD(+) group. This finding has led us to believe that hemodynamic alterations may also cause CCD rather than a functional disruption alone. In general, BOLD imaging enables investigations on resting-state functional connectivity and the influence of CCD-induced altered metabolism in patients with stroke.5

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Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis

In the article "BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis," Sebök et al. reported similar sensitivity of blood oxygen level–dependent cerebrovascular reactivity (BOLD-CVR) in detecting crossed cerebellar diaschisis (CCD) as compared to (15O)-H_2O-PET in 25 participants with symptomatic unilateral cerebrovascular steno-occlusive disease and reported that those with CCD had poorer baseline neurologic performance and 3-month neurologic outcome. In response, Reidler et al. question whether CCD was the cause of consequence of poor outcomes, noting that it may be an epiphenomenon of large-volume supratentorial strokes and citing conflicting evidence in the literature about independent association of CCD with post-stroke outcomes. They suggest accounting for lesion volume and distribution in the analyses. In their reply, Niftrik et al. agree that their finding of worse outcome in those with CCD should be cautiously interpreted and investigated in follow-up studies, but argue that supratentorial stroke volume is an inexact measurement, although stroke location would be helpful to examine. They clarify their finding of impaired supratentorial BOLD-CVR in the group with CCD and opine that hemodynamic changes may cause CCD rather than just functional disruption.

Aravind Ganesh, MD, and Steven Galetta, MD
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Reader response: BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis

Paul Reidler (Munich) and Wolfgang G. Kunz (Munich)
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We read with great interest the article by Sebök et al.[1] on the detection of crossed cerebellar diaschisis (CCD) in subacute and chronic stroke using blood oxygen level-dependent (BOLD)-MRI. They observed that patients with signs of CCD had poorer neurologic function at baseline and at 3 months. However, because adjusted analysis is lacking, it remains unclear whether CCD was the cause or consequence of poor outcomes.

The phenomenon of CCD, especially in the acute phase, is highly associated with large-volume supratentorial stroke.[2,3] Acute CCD had no independent impact on outcome and may be an epiphenomenon of large-volume strokes.[2] Correlations of chronic CCD with worse outcome have been reported, yet adjustments were not made for confounders.[4,5] In the current study, inferior cerebrovascular response indicated more severe supratentorial lesions in the CCD+ group, yet lesion volumes were not specified.[1] Because lesion volume and distribution affect outcome, group comparisons should be interpreted with caution concerning a CCD-outcome relationship. The final infarct size and location would provide additional insight on this matter.

Author disclosures are available upon request (journal@neurology.org).

Of interest, CCD has been linked to BOLD signal change, a measure of neuronal metabolism and activity. This is encouraging for future studies relating resting-state functional connectivity and CCD status.

1. Sebök M, van Niftrik CHB, Piccirelli M, et al. BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis. Neurology 2018;91:e1328–e1337.
2. Kunz WG, Sommer WH, Hohne C, et al. Crossed cerebellar diaschisis in acute ischemic stroke: impact on morphologic and functional outcome. J Cereb Blood Flow Metab 2017;37:3615–3624.
3. Kang KM, Sohn CH, Choi SH, et al. Detection of crossed cerebellar diaschisis in hyperacute ischemic stroke using arterial spin-labeled MR imaging. PLoS One 2017;12:e0173971.
4. Sobesky J, Thiel A, Ghaemi M, et al. Crossed cerebellar diaschisis in acute human stroke: a PET study of serial changes and response to supratentorial reperfusion. J Cereb Blood Flow Metab 2005;25:1685–1691.
5. Takasawa M, Watanabe M, Yamamoto S, et al. Prognostic value of subacute crossed cerebellar diaschisis: single-photon emission CT study in patients with middle cerebral artery territory infarct. AJNR Am J Neuroradiol 2002;23:189–193.

Author response: BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis

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We kindly thank Drs. Reidler and Kunz for their insightful comments regarding our article.[1] The main objective was to study blood oxygen level–dependent cerebrovascular reactivity (BOLD-CVR) for crossed cerebellar diaschisis (CCD) detection. In this regard, worse clinical outcome in the CCD(+) group should indeed be interpreted with caution. Ideally, this association needs to be further investigated in a uniform stroke cohort with sequential follow-up studies.

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The statement made by Drs. Reidler and Kunz about "inferior cerebrovascular response indicating more severe supratentorial lesions" is, however, erroneous. We have only shown the presence of more impaired supratentorial BOLD-CVR in the CCD(+) group. This finding has led us to believe that hemodynamic alterations may also cause CCD rather than a functional disruption alone. In general, BOLD imaging enables investigations on resting-state functional connectivity and the influence of CCD-induced altered metabolism in patients with stroke.[5]

1. Sebok M, van Niftrik CHB, Piccirelli M, et al. BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis. Neurology 2018;91:e1328–e1337.
2. Cassidy JM, Tran G, Quinlan EB, Cramer SC. Neuroimaging identifies patients most likely to respond to a restorative stroke therapy. Stroke 2018;49:433–438.
3. Kang KM, Sohn CH, Choi SH, et al. Detection of crossed cerebellar diaschisis in hyperacute ischemic stroke using arterial spin-labeled MR imaging. PLoS One 2017;12:e0173971.
4. Kunz WG, Sommer WH, Höhne C, et al. Crossed cerebellar diaschisis in acute ischemic stroke: impact on morphologic and functional outcome. J Cereb Blood Flow Metab 2017;37:3615–3624.
5. Van Niftrik CHB, Sebok M, Muscas G, et al. Characterizing ipsilateral thalamic diaschisis in symptomatic cerebrovascular steno-occlusive patients. J Cereb Blood Flow Metab 2019;12:271678x19830532.

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Editors' note: Pearls & Oy-sters: Pembrolizumab-induced myasthenia gravis

In the article "Pearls & Oy-sters: Pembrolizumab-induced myasthenia gravis," Algaeed et al. presented a 73-year-old man who was diagnosed with myasthenia gravis (MG) after receiving pembrolizumab for recurrent melanoma and had positive anti–acetylcholine receptor antibodies (AChRAbs). In response, Robbins et al. note that antibodies like AChRAbs may be less specific for MG after immune checkpoint inhibitor (ICI) therapy and may be a marker for general autoimmunity. They note that AChRAb-positive patients receiving ICI therapy are more likely to develop myositis and that this can clinically resemble MG. In this regard, they note that some reports of ICI-associated MG had normal repetitive nerve stimulation and single-fiber EMG despite severe weakness. Using an illustrative case, they note that the distinction between myositis and MG has important implications for clinical management. In response, Algaeed et al. acknowledge these observations, but note that their patient had unequivocal fatigable ptosis strongly supporting (not pathognomonic in the editor's opinion) the diagnosis of MG. The authors also argue that further understanding of ICI-related autoimmune pathogenesis is needed before concluding that AChRAbs can just be a marker of general autoimmunity.

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Reader response: Pearls & Oy-sters: Pembrolizumab-induced myasthenia gravis

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We read with interest the Resident & Fellow Pearls & Oy-sters article by Algaeed et al.[1] on immune checkpoint inhibitor (ICI)-associated myasthenia gravis (MG). Antibodies such as anti–acetylcholine receptor antibodies (AChRAbs) may be less specific for MG after ICI therapy.[2] Positive antibodies may be a marker for autoimmunity in general rather than MG specifically; individuals with thymoma receiving ICI therapy who are AChRAb positive pre-treatment are more likely to develop myositis, even without evidence of neuromuscular junction (NMJ) disease.[2] Complicating the picture, ICI-associated myositis clinically resembles MG, having a predilection for the oculobulbar and respiratory musculature, and the 2 conditions can overlap.[3,4]

We recently admitted a patient with metastatic melanoma who developed concurrent myositis and myocarditis just 2 weeks after a single nivolumab dose. He was initially diagnosed with MG due to ptosis, ophthalmoparesis, and bulborespiratory weakness. However, arguing against NMJ pathology, AChRAbs and muscle-specific kinase antibodies were negative, repetitive nerve stimulation (RNS) was repeatedly negative despite severe weakness, and pyridostigmine was ineffective. Other reports of ICI-associated MG also had normal RNS and single-fiber EMG despite severe weakness.[5] Our patient refused biopsy, opting for comfort measures, but similar patients have pathology-demonstrated inflammatory myositis.[4] The distinction between myositis and MG is not trivial because ongoing weakness (despite normalized creatine phosphokinase [CPK]) may require treatment escalation in MG; in myositis, ongoing weakness may reflect fibrofatty muscle replacement where recovery can lag behind CPK normalization.

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Tacrolimus or cyclosporine may be useful in ICI-induced myositis when steroids and IV immunoglobulin are insufficient, although a formal study is needed. Because immune-mediated neuromuscular disease after ICI treatment is less rare than the authors implied,[3,4] clinicians must learn to distinguish MG from ICI-induced myositis in these cases—understanding that antibody positivity does not equal NMJ disease.[2]

1. Algaeed M, Mukharesh L, Heinzelmann M, Kaminski HJ. Pearls & Oy-sters: pembrolizumab-induced myasthenia gravis. Neurology 2018;91:e1365–e1367.
2. Mammen AL, Rajan A, Pak K, et al. Pre-existing antiacetylcholine receptor autoantibodies and B cell lymphopaenia are associated with the development of myositis in patients with thymoma treated with avelumab, an immune checkpoint inhibitor targeting programmed death-ligand 1. Ann Rheum Dis 2019;78:150–152.
3. Suzuki S, Ishikawa N, Konoeda F, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology 2017;89:1127–1134.
4. Liewluck T, Kao JC, Mauermann ML. PD-1 inhibitor-associated myopathies: emerging immune-mediated myopathies. J Immunother 2018;41:208–211.
5. Tan RYC, Toh CK, Takano A. Continued response to one dose of nivolumab complicated by myasthenic crisis and myositis. J Thorac Oncol 2017;12:e90–e91.

Author response: Pearls & Oy-sters: Pembrolizumab-induced myasthenia gravis

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Robbins et al. provide critically important observations regarding the complexity of checkpoint inhibitor–associated autoimmunity—in particular, overlap of autoimmune diseases, specifically myasthenia gravis. In our patient,[1] there were unequivocal signs of ptosis with fatigue, which are pathognomonic for myasthenia gravis. There needs to be much greater understanding of checkpoint inhibitor autoimmune pathogenesis before making the conclusion that the acetylcholine receptor autoantibodies are a simple marker of autoimmunity, rather than being evidence of myasthenia gravis. The acetylcholine receptor–binding antibody is among the most specific tests for any disease, except with the rare exception of thymoma, as noted by Robbins et al., and some pregnant women.[2] Repetitive stimulation has relatively low sensitivity; although single-fiber examination is better, it can often be negative in patients with myasthenia gravis.[3]

We can all agree that neurologists must be vigilant in rapid identification and treatment of neuromuscular diseases in the context of checkpoint inhibitor therapies. Even case reports will be valuable in clarifying the presentation of these diseases.

1. Algaeed M, Mukharesh L, Heinzelmann M, Kaminski HJ. Pearls & Oy-sters: pembrolizumab-induced myasthenia gravis. Neurology 2018;91:e1365–e1367.
2. Leite MI, Waters P, Vincent A. Diagnostic use of autoantibodies in myasthenia gravis. Autoimmunity 2010;43:371–379.
3. Benatar M, Hammad M, Doss-Riney H. Concentric-needle single-fiber electromyography for the diagnosis of myasthenia gravis. Muscle Nerve 2006;34:163–168.

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